Organic LETTERS

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Modular, Step-Efficient Palladium-Catalyzed Cross-Coupling Strategy To Access C6-Heteroaryl 2-Aminopurine Ribonucleosides

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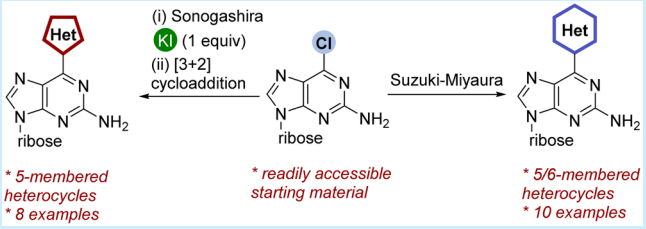
Supporting Information

ABSTRACT: Two Pd-catalyzed methods to access 6-heteroaryl 2-aminopurine ribonucleosides from 6-chloroguanosine are described. First, Pd-132-catalyzed Suzuki–Miyaura cross-coupling using a series of boron substrates and 6-chloroguanosine forms 6-heteroaryl-2-aminopurines in a single step. The versatility of 6-chloroguanosine is further demonstrated using a modified Sonogashira coupling employing potassium iodide as an additive. Finally, the utility of the 6-alkynyl-2-aminopurine ribonucleoside as a dipolarophile in [3 + 2] cycloadditions is presented, affording triazoles and isoxazoles when reacted with azide and isonitrile 1,3-dipoles, respectively.

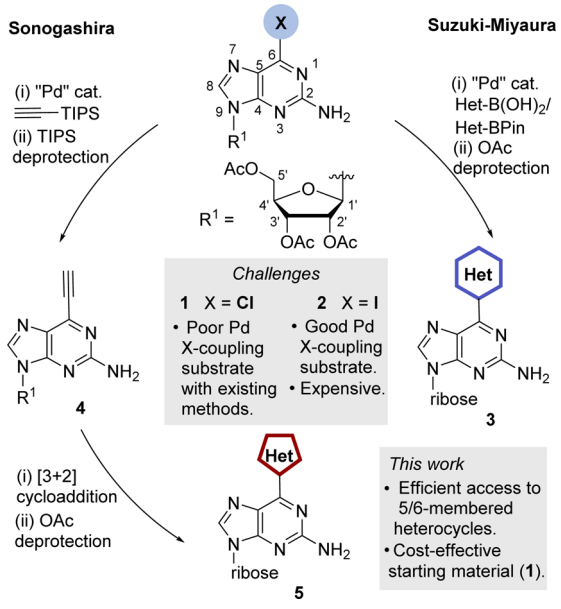


Nucleoside analogues are essential molecules for both clinical and basic research. To date, there are over 30 nucleoside analogues approved for use as antiviral or cytotoxic agents, with almost 50% of these analogues containing modifications to the natural pyrimidine/purine base.[1] Additionally, base-modified ribonucleosides offer considerable opportunities to enhance the efficacy and cellular uptake properties of therapeutic oligoribonucleotides.[2,3] Apart from clinical applications, base-derivatized nucleoside analogues are important biotechnological tools for probing fundamental DNA and RNA biology[4−6] and for synthetic biology applications.[7−12] Consequently, there is a pressing need for the development of cost-effective synthetic routes that facilitate access to novel nucleoside building blocks.

The 6-position of purines is a prime modification site for many of these applications.[13] Current methods have predominantly focused on C6-arylation of adenosine ribo- and deoxyribonucleosides.[14−24] In contrast, efficient access to C6-heteroaryl guanosines,[25,26] especially protocols that utilize a cost-effective coupling partner, such as **1**, are notably limited (Scheme 1).[25−29] One key structural difference between adenosine and guanosine nucleobases that has the potential to have a significant impact on the success of Pd-catalyzed cross-couplings is the presence of the N2 exocyclic amine. Heterocycles containing exocyclic amines are traditionally challenging substrates for Suzuki–Miyaura cross-couplings, resulting in variable product yields and the need for the development of bespoke reaction conditions.[30]

Thus, a challenge in the nucleoside synthetic arena is to develop a general set of conditions to prepare 6-heteroaryl guanosines from cost-effective substrates, such as **1**. Previous mechanistic studies of Suzuki–Miyaura couplings with heteroaryl chlorides have shown that oxidative addition across

Scheme 1. Modular and Step-Efficient Access to 6-Heteroaryl Guanosine Analogues



Het–Cl bonds can result in the formation of nonproductive and catalytically inactive [Pd–Cl] intermediates.[30] To circumvent this problem, current strategies that have been developed for the preparation of 6-heteroaryl guanosines require the use of the expensive 6-iodo-2-aminoguanosine (**2**) substrate,[26,28,31] prepared from **1** via Finkelstein reaction.[32]

Received: May 27, 2017
Published: July 6, 2017

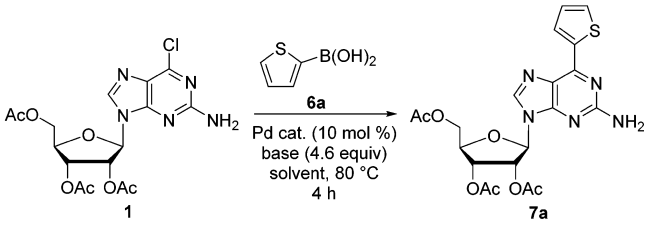
DOI: 10.1021/acs.orglett.7b01602
Org. Lett. 2017, 19, 3759−3762

Cross-coupling strategies such as Stille,[33−35] Negishi,[36−38] and other bespoke variants[39,40] of these have been explored using both **1** and **2**. However, the toxicity associated with organotin reagents and the presence of a number of Lewis basic sites and electrophilic O-protecting groups have limited their broader utility.

Herein, we show that **1** can be used as a general coupling partner for the preparation of C6-heteroarylated guanosine analogues (**3**) via, for example, a Pd-132-catalyzed Suzuki−Miyaura cross-coupling methodology (Scheme 1). Furthermore, we demonstrate the utility of **1** as a substrate for Sonogashira cross-couplings.[14,18,41−43] Finally, we showcase the general utility of alkyne **4** as a dipolarophile in [3 + 2] cycloadditions with azide and isonitrile 1,3-dipoles to prepare 6-heteroaryl guanosines (**5**) comprising 1,4-triazole and isoxazole units, respectively.

To establish optimal Suzuki−Miyaura coupling conditions, we used **1** and the boronic acid **6a** as our exemplar reagent set. Exploration of reaction conditions recently developed for Suzuki−Miyaura cross-couplings with nucleoside heteroaryl organoborons and aryl iodides afforded product **7a** in 58% yield (entry 1, Table 1).[44] Altering the solvent had a minimal impact

Table 1. Optimization of Suzuki−Miyaura Coupling



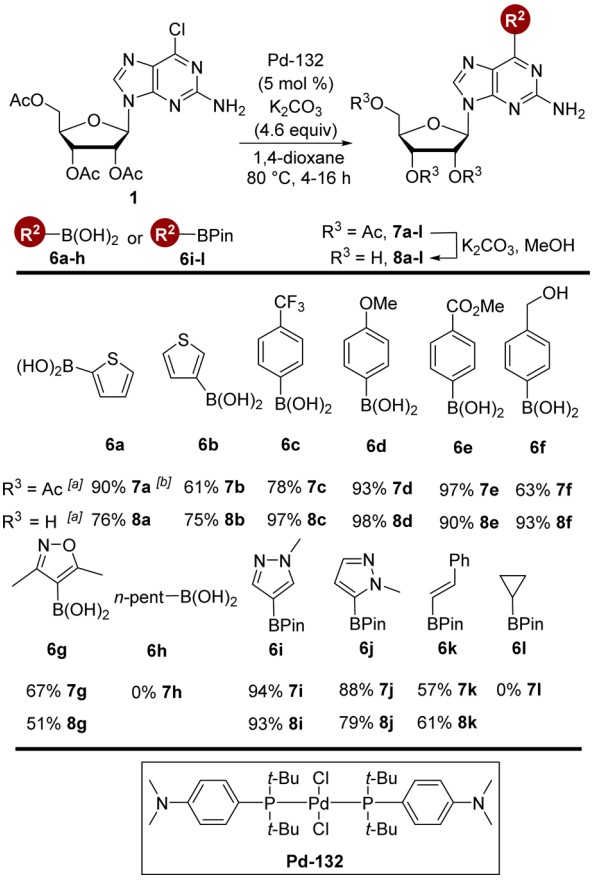
entry	solvent	base	Pd catalyst	yield[a] (%)
1	DMF	K_2CO_3	$Pd(dppf)Cl_2$	58
2	DMSO	K_2CO_3	$Pd(dppf)Cl_2$	64
3	1,4-dioxane	K_2CO_3	$Pd(dppf)Cl_2$	54
4	DMF	K_2CO_3	Pd-132	85
5	DMSO	K_2CO_3	Pd-132	69
6	**1,4-dioxane**	**K_2CO_3**	**Pd-132**	**90**
7	DMF	KOAc	Pd-132	80
8	DMSO	KOAc	Pd-132	81
9	1,4-dioxane	KOAc	Pd-132	80
10	DMF	K_3PO_4	Pd-132	51
11	DMSO	K_3PO_4	Pd-132	66
12	1,4-dioxane	K_3PO_4	Pd-132	50
13	DMF	KF on alumina	Pd-132	59
14	DMSO	KF on alumina	Pd-132	73
15	1,4-dioxane	KF on alumina	Pd-132	67

[a]Isolated yields.

on the yield of **7a** using catalytic $Pd(dppf)Cl_2$ and K_2CO_3 as the base (entries 2 and 3, Table 1), whereas changing the Pd catalyst to Pd-132[45,46] resulted in a marked increase in the yield of **7a** (85%, entry 4, Table 1). After an extensive survey of base and solvent (entries 4−15, Table 1, Figure S1), the optimal set of conditions identified for this reaction were catalytic Pd-132 (10 mol %) and K_2CO_3 in 1,4-dioxane (90% isolated yield of **7a**, entry 6, Table 1).

The utility of **1** as a general substrate for Suzuki−Miyaura couplings was then explored using a series of boronic acids and Bpin esters (**6a−l**, Scheme 2). Each of the sp^2−sp^2 couplings afforded the desired products **7a−g,i−k** in 57−97% yield,

Scheme 2. Scope of the Suzuki−Miyaura Cross-Coupling Using 1



[a]Isolated yields. [b]92% yield on 1 mmol scale.

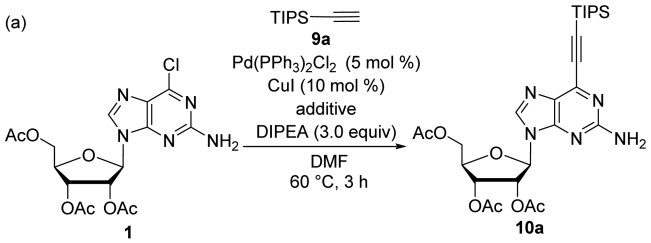
which surveyed a range of electron-rich and electron-poor aryl and heteroaryl boron species. Unfortunately, sp^3−sp^2 couplings employing substrates **6h,l** resulted in the recovery of starting material from the crude mixture. The addition of Ag_2O to the reaction with **6l** again resulted in no reaction and no consumption of **1**.[47] Acetyl deprotection of **7a−g,i−k** using K_2CO_3/MeOH afforded the corresponding free nucleosides **8a−g,i−k**. To expand the diversity of heteroaryl substituents available for installation at the 6-position, we explored the utility of **1** in Sonogashira cross-couplings with TIPS-acetylene (**9a**, Figure 1).

A well-established phenomenon is that the Sonogashira reaction generally functions best when a (hetero)aryl iodide is used as a coupling partner.[48] Indeed, coupling of acetyl-protected 6-iodoguanosine (**2**) with **9a** using catalytic $Pd(PPh_3)Cl_2$/CuI produced **10a** in 93% yield (Scheme S1).[49] Under similar conditions, only 36% yield of **10a** was obtained when **1** was used as the corresponding substrate (entry 1, Figure 1a). When $Pd(PPh_3)Cl_2$ was replaced with Pd-132 (i.e., 5% Pd-132), the yield of **10a** dropped to 21% (Figure S2). We surmised that the addition of an iodide source to the reaction mixture would circumvent the need to prepare **2**.[48,50]

A variety of iodide salts were evaluated using a benchmark set of conditions [i.e., 5 mol % of $Pd(PPh_3)Cl_2$, 10 mol % of CuI, DIPEA, DMF; Figure 1a and Figure S2]. The addition of 1 equiv of alkali metal iodides (i.e., NaI, KI, CsI) resulted in a significant increase in the yield of **10a**; going from 36% (i.e., no iodide additive, entry 1) to 76 (NaI), 86 (KI), and 79% (CsI)

DOI: 10.1021/acs.orglett.7b01602
Org. Lett. 2017, 19, 3759−3762

(a)



entry	iodide additive	equivalents of iodide	yield (%)[a]
1	-	-	36
2	LiI	1	29
3	NaI	1	76
4	**KI**	**1**	**86**
5	KI	0.5	69
6	KI	0.1	55
7	CsI	1	79
8	TBAI	1	22
9	CuI	1	5
10	18-Crown-6	1	23
11	KI/18-Crown-6	1/1	21
12	KI/(-CuI)	1	2
13	KCl	1	27

(b)

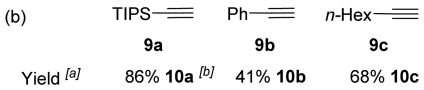


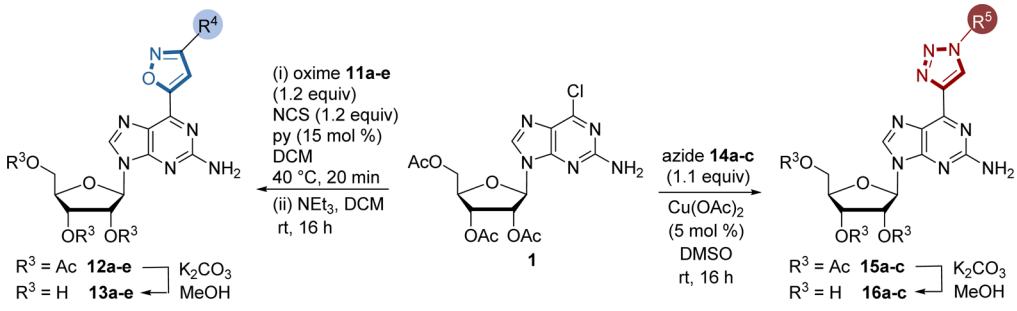
Figure 1. (a) Optimization of Sonogashira cross-coupling. (b) Substrate scope of Sonogashira cross-coupling of **1** using optimized conditions (entry 4). [a]Isolated yields. [b]Compound **10a** obtained in 80% yield when conducted on a 1 mmol scale.

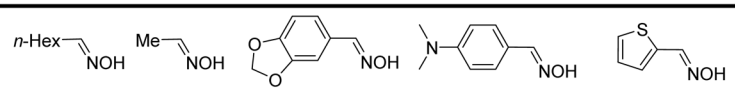
(entries 3, 4, and 7, Figure 1a). Decreasing the equivalents of KI to substoichiometric quantities resulted in a drop in the yield of **10a**, which is indicative of the need for a stoichiometric iodide source (entries 4–6, Figure 1a; Figure S2). This was further confirmed when KCl replaced KI, producing **10a** in only 27% yield (entry 13, Figure 1a). These optimized conditions were then shown to be compatible with aromatic (**9b**) and aliphatic (**9c**) alkynes, producing **10b** and **10c** (Figure 1b).

We finally sought to explore the utility of alkyne **4** as a dipolarophile in [3 + 2] cycloaddition reactions. TIPS deprotection of **10a** using polymer-supported fluoride produced **4** in 78% yield (see Supporting Information). Using **4**, a suite of isoxazole and triazole-substituted analogues **12a–e**/**15a–c** were prepared. Both alkyl and aromatic oximes were tolerated, producing isoxazoles **12a–e** in 28–67% yield. Azides **14a–c** formed 1,4-triazoles **15a–c** in 21–83% yield under CuAAC conditions. Due to the nitrogen-rich and polar scaffold of these triazoles, the purification of these compounds required RP-HPLC. Finally, deprotection of the isoxazole and triazole series with K_2CO_3/MeOH afforded **13a–e** and **16a–c**, respectively (Scheme 3).

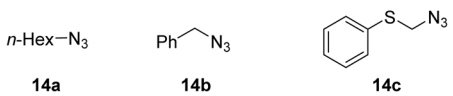
In summary, we have developed modular, step-efficient methodologies for rapid access to a suite of 18 C6-heteroaryl-functionalized 2-aminopurine nucleosides from the cost-effective 6-chloroguanosine precursor. Pd-132-catalyzed Suzuki–Miyaura coupling provides aryl and heteroaryl nucleosides in two steps from **1**, whereas five-membered heteroaryl variants were prepared in four steps via a single alkyne intermediate **10a**. We envisage that the utility of our synthetic approach will expand the development of guanosine-based analogues for therapeutic or synthetic biology applications.

Scheme 3. Modular Formation of Isoxazole and Triazole Nucleosides from 4





	11a	11b	11c	11d	11e
R^3 = Ac [a]	64% **12a**	67% **12b**	46% **12c**	31% **12d**	28% **12e**
R^3 = H [a]	85% **13a**	83% **13b**	26% **13c**	44% **13d**	63% **13e**



	14a	14b	14c
R^3 = Ac [a]	83% **15a**	21% **15b**	64% **15c** [b]
R^3 = H [a]	74% **16a**	82% **16b**	35% **16c**

[a]Isolated yields. [b]55% yield on a 1 mmol scale.

DOI: 10.1021/acs.orglett.7b01602
Org. Lett. 2017, 19, 3759–3762

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01602.

Experimental procedures and characterization data for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by an EPSRC-GSK industrial CASE studentship for H.B., a University studentship for T.D.K., and postdoctoral funding for S.P. by the Leverhulme Trust (RPG-2014-313). We thank the EPSRC U.K. National Mass Spectrometry Facility at Swansea University for HRMS analyses of compounds.

■ REFERENCES

(1) Jordheim, L. P.; Durantel, D.; Zoulim, F.; Dumontet, C. *Nat. Rev. Drug Discovery* **2013**, *12*, 447.

(2) Warren, L.; Manos, P. D.; Ahfeldt, T.; Loh, Y.-H.; Li, H.; Lau, F.; Ebina, W.; Mandal, P. K.; Smith, Z. D.; Meissner, A.; Daley, G. Q.; Brack, A. S.; Collins, J. J.; Cowan, C.; Schlaeger, T. M.; Rossi, D. J. *Cell Stem Cell* **2010**, *7*, 618.

(3) Andries, O.; Mc Cafferty, S.; De Smedt, S. C.; Weiss, R.; Sanders, N. N.; Kitada, T. *J. Controlled Release* **2015**, *217*, 337.

(4) Strobel, S. A.; Shetty, K. *Proc. Natl. Acad. Sci. U. S. A.* **1997**, *94*, 2903.

(5) König, J.; Zarnack, K.; Luscombe, N. M.; Ule, J. *Nat. Rev. Genet.* **2012**, *13*, 77.

(6) Chaulk, S. G.; MacMillan, A. M. *Nat. Protoc.* **2007**, *2*, 1052.

(7) Reichenbach, L. F.; Sobri, A. A.; Zaccai, N. R.; Agnew, C.; Burton, N.; Eperon, L. P.; de Ornellas, S.; Eperon, I. C.; Brady, R. L.; Burley, G. A. *Chem.* **2016**, *1*, 946.

(8) Kimoto, M.; Mitsui, T.; Yokoyama, S.; Hirao, I. *J. Am. Chem. Soc.* **2010**, *132*, 4988.

(9) Hikida, Y.; Kimoto, M.; Yokoyama, S.; Hirao, I. *Nat. Protoc.* **2010**, *5*, 1312.

(10) Kimoto, M.; Kawai, R.; Mitsui, T.; Yokoyama, S.; Hirao, I. *Nucleic Acids Res.* **2009**, *37*, e14.

(11) Malyshev, D. A.; Dhami, K.; Lavergne, T.; Chen, T.; Dai, N.; Foster, J. M.; Correa, I. R., Jr.; Romesberg, F. E. *Nature* **2014**, *509*, 385.

(12) Zhang, Y.; Lamb, B. M.; Feldman, A. W.; Zhou, A. X.; Lavergne, T.; Li, L.; Romesberg, F. E. *Proc. Natl. Acad. Sci. U. S. A.* **2017**, *114*, 1317.

(13) Hocek, M.; Fojta, M. *Chem. Soc. Rev.* **2011**, *40*, 5802.

(14) Hocek, M.; Naus, P.; Pohl, R.; Votruba, I.; Furman, P. A.; Tharnish, P. M.; Otto, M. J. *J. Med. Chem.* **2005**, *48*, 5869.

(15) Taherpour, S.; Golubev, O.; Lonnberg, T. *J. Org. Chem.* **2014**, *79*, 8990.

(16) Amiable, C.; Paoletti, J.; Haouz, A.; Padilla, A.; Labesse, G.; Kaminski, P.-A.; Pochet, S. *Eur. J. Med. Chem.* **2014**, *85*, 418.

(17) Hassan, A. E. A.; Abou-Elkhair, R. A. I.; Riordan, J. M.; Allan, P. W.; Parker, W. B.; Khare, R.; Waud, W. R.; Montgomery, J. A.; Secrist, J. A., III. *Eur. J. Med. Chem.* **2012**, *47*, 167.

(18) Mathew, S. C.; By, Y.; Berthault, A.; Virolleaud, M.-A.; Carrega, L.; Chouraqui, G.; Commeiras, L.; Condo, J.; Attolini, M.; Gaudel-Siri, A.; Ruf, J.; Rodriguez, J.; Parrain, J.-L.; Guieu, R. *Org. Biomol. Chem.* **2010**, *8*, 3874.

(19) Heuberger, B. D.; Shin, D.; Switzer, C. *Org. Lett.* **2008**, *10*, 1091.

(20) Bambuch, V.; Pohl, R.; Hocek, M. *Eur. J. Org. Chem.* **2008**, *2008*, 2783.

(21) Bae, S.; Lakshman, M. K. *J. Org. Chem.* **2008**, *73*, 1311.

(22) Bae, S.; Lakshman, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 782.

(23) Veliz, E. A.; Beal, P. A. *J. Org. Chem.* **2001**, *66*, 8592.

(24) Lakshman, M. K.; Hilmer, J. H.; Martin, J. Q.; Keeler, J. C.; Dinh, Y. Q. V.; Ngassa, F. N.; Russon, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 7779.

(25) Lakshman, M. K.; Gunda, P.; Pradhan, P. *J. Org. Chem.* **2005**, *70*, 10329.

(26) Hocek, M.; Holy, A.; Votruba, I.; Dvorakova, H. *J. Med. Chem.* **2000**, *43*, 1817.

(27) Lakshman, M. K.; Thomson, P. F.; Nuqui, M. A.; Hilmer, J. H.; Sevova, N.; Boggess, B. *Org. Lett.* **2002**, *4*, 1479.

(28) Qu, G. R.; Xin, P. Y.; Niu, H. Y.; Jin, X.; Guo, X. T.; Yang, X. N.; Guo, H. M. *Tetrahedron* **2011**, *67*, 9099.

(29) Lakshman, M. K.; Frank, J. *Org. Biomol. Chem.* **2009**, *7*, 2933.

(30) Düfert, M. A.; Billingsley, K. L.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 12877.

(31) Havelkova, M.; Dvorak, D.; Hocek, M. *Synthesis* **2001**, *2001*, 1704.

(32) Liu, J.; Janeba, Z.; Robins, M. J. *Org. Lett.* **2004**, *6*, 2917.

(33) Ren, H.; An, H.; Hatala, P. J.; Stevens, W. C., Jr.; Tao, J.; He, B. *Beilstein J. Org. Chem.* **2015**, *11*, 2509.

(34) James, D.; Escudier, J.-M.; Szlosek-Pinaud, M.; Fouquet, E. *Molecules* **2013**, *18*, 13654.

(35) Naus, P.; Perlikova, P.; Bourderioux, A.; Pohl, R.; Slavetinska, L.; Votruba, I.; Bahador, G.; Birkus, G.; Cihlar, T.; Hocek, M. *Bioorg. Med. Chem.* **2012**, *20*, 5202.

(36) Wang, D.-C.; Niu, H.-Y.; Qu, G.-R.; Liang, L.; Wei, X.-J.; Zhang, Y.; Guo, H.-M. *Org. Biomol. Chem.* **2011**, *9*, 7663.

(37) Gundersen, L.-L. *Targets Heterocycl. Syst.* **2008**, *12*, 85.

(38) Silhar, P.; Pohl, R.; Votruba, I.; Hocek, M. *Collect. Czech. Chem. Commun.* **2005**, *70*, 1669.

(39) Bhanu Prasad, A. S.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P. *Tetrahedron* **1997**, *53*, 7237.

(40) Stevenson, T. M.; Prasad, A. S. B.; Citineni, J. R.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 8375.

(41) Pu, X.; Li, H.; Colacot, T. J. *J. Org. Chem.* **2013**, *78*, 568.

(42) Yang, Y.; Chew, X.; Johannes, C. W.; Robins, E. G.; Jong, H.; Lim, Y. H. *Eur. J. Org. Chem.* **2014**, *2014*, 7184.

(43) Milburn, R. R.; Thiel, O. R.; Achmatowicz, M.; Wang, X.; Zigterman, J.; Bernard, C.; Colyer, J. T.; DiVirgilio, E.; Crockett, R.; Correll, T. L.; Nagapudi, K.; Ranganathan, K.; Hedley, S. J.; Allgeier, A.; Larsen, R. D. *Org. Process Res. Dev.* **2011**, *15*, 31.

(44) Klecka, M.; Pohl, R.; Klepetarova, B.; Hocek, M. *Org. Biomol. Chem.* **2009**, *7*, 866.

(45) Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104.

(46) Guram, A. S.; King, A. O.; Allen, J. G.; Wang, X.; Schenkel, L. B.; Chan, J.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J.; Reider, P. J. *Org. Lett.* **2006**, *8*, 1787.

(47) Zou, G.; Reddy, Y. K.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 7213.

(48) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

(49) Matsuda, A.; Shinozaki, M.; Yamaguchi, T.; Homma, H.; Nomoto, R.; Miyasaka, T.; Watanabe, Y.; Abiru, T. *J. Med. Chem.* **1992**, *35*, 241.

(50) Thathagar, M. B.; Rothenberg, G. *Org. Biomol. Chem.* **2006**, *4*, 111.

DOI: 10.1021/acs.orglett.7b01602
Org. Lett. 2017, 19, 3759−3762